

Hypertension Editors' Picks Pregnancy, Hypertension, and Preeclampsia

The Editors

The following articles are being highlighted as part of *Hypertension's* Editors' Picks Series. During the last decade, there has been a surge in the interest in identifying and characterizing new pathways that lead to new onset hypertension during pregnancy. Novel animal models have been reported that should aid in the development of targeted therapies for preeclampsia. Several innovative biomarkers have been identified in humans and tested for use in prediction and diagnosis of preeclampsia and its complications. Hypertensive complications of pregnancy have also emerged as major risk factors for hypertension and cardiovascular disease in the mother and the offspring.

We have collated for our readers all 45 full length basic and clinical articles on pregnancy and preeclampsia published in our Journal between January 2013 and January 2014. It is quite obvious from the articles listed that *Hypertension*, an American Heart Association Journal, has become an important home for the publication of high quality studies on pregnancy and preeclampsia.

Matrix Metalloproteinase Enhances Big-Endothelin-1 Constriction in Mesenteric Vessels of Pregnant Rats With Reduced Uterine Blood Flow¹

Abstract

Preeclampsia is a leading cause of maternal and fetal morbidity/mortality; however, the pathophysiological mechanisms are poorly understood. Vascular endothelial dysfunction in preeclampsia has been partially attributed to changes in endothelin-1 (ET-1). Several enzymes, including matrix metalloproteinases (MMPs, particularly MMP-2), cleave the inactive precursor bigET-1 (bET-1) to active ET-1. Notably, expression levels of MMP-2 have been shown to be increased in women who subsequently develop preeclampsia. We hypothesized that increased MMP-2 expression leads to increased bET-1 conversion, thus increasing vasoconstriction in preeclampsia. A reduced uteroplacental perfusion pressure (RUPP) model of preeclampsia in the rat was used to assess mesenteric artery vascular function. Responses to bET-1 (3–310 nmol/L) and ET-1 (1–200 nmol/L) were studied in the presence or absence of enzyme inhibitors known to cleave bET-1. Vascular contractility in response to bET-1 was greater in RUPP than Sham ($P < 0.0001$), while neither responses to ET-1 nor maximal contractility to high potassium salt solution (KPSS, 123.70 mmol/L) were different. MMP inhibition with GM6001 (30 μ mol/L) significantly decreased responses to bET-1 in RUPP ($P < 0.0001$) but not Sham-operated rats. Interestingly, combined treatment with GM6001 and L-NAME (100 μ mol/L) revealed a nitric oxide modulation of MMPs that was reduced in RUPP. In summary, we found increased vascular contractility to bET-1 in the RUPP model of preeclampsia that was likely attributable to upstream enzymatic pathways. These data are consistent with a greater contribution of MMP to cleavage of bET-1 to ET-1 *ex vivo* in RUPP, suggesting that this enzyme may be partially responsible for increased bET-1 induced contractility.

The Impact of Malaria in Pregnancy on Changes in Blood Pressure in Children During Their First Year of Life²

Abstract

We established a maternal-birth cohort in Ibadan, Nigeria where malaria is hyperendemic to assess how intrauterine exposure to malaria affected infant blood pressure (BP) development. In a local maternity hospital, healthy pregnant women had regular blood films for malaria parasites from booking to delivery. Growth and BP were measured on 318 babies, all followed from birth to 3 and 12 months. Main outcomes were standardised measures of anthropometry and change in BP to 1 year. Babies exposed to maternal malaria were globally smaller at birth and boys remained smaller at 3 months and 1 year. Change in systolic BP (SBP) over the year was greater in boys than girls (20.9 vs 15.7 mmHg $P = 0.002$) but greater in girls exposed to maternal malaria (18.7 vs 12.7, 1–11, mmHg, $P = 0.02$). 11% of boys (> twice expected) had a SBP >95th percentile (hypertensive, US criteria) of whom 68% had maternal malaria exposure. On regression analysis (β coefficients, mmHg), gender (boys > girls, $\beta = 4.4$, 1.1–7.7; $P = 0.01$), maternal malaria exposure (3.64, 0.3–6.9, $P = 0.03$) and weight change (2.4, 0.98 to 3.8 /1 SDS; $P = 0.001$) all independently increased SBP change to 1 year, while increase in length decreased SBP (-1.98, -3.6 to -0.40). In conclusion, malaria-exposed boys had excess 'hypertension,' exposed girls a greater increase in SBP. Intrauterine exposure to malaria had gender-dependent effects on BP, independent of infant growth. As infant-child-adult BP tracking is powerful, a malarial effect may contribute to the African burden of hypertension.

Pravastatin Attenuates Hypertension, Oxidative Stress, and Angiogenic Imbalance in Rat Model of Placental Ischemia-Induced Hypertension³

Abstract

Preeclampsia is a pregnancy-specific condition characterized by an imbalance of circulating angiogenic factors and new-onset hypertension. Although current treatment options are limited, recent studies suggest pravastatin may improve angiogenic profile and reduce blood pressure in preeclampsia. We hypothesized pravastatin would restore angiogenic balance and reduce mean arterial pressure (MAP) in rats with reduced utero-placental perfusion pressure (RUPP)-induced hypertension. Pravastatin was administered i.p. (1 mg/kg/day) in RUPP (RUPP+P) and normal pregnant rats (NP+P) from day 14–19 of pregnancy. On day 19, MAP was measured via catheter, conceptus data was recorded and tissues collected. MAP was increased ($P<0.05$) in RUPP compared to NP dams and pravastatin ameliorated this difference. Pravastatin attenuated decreased fetal weight and plasma VEGF and the RUPP-induced increased sFlt-1 when compared to NP dams. Pravastatin treatment did not improve angiogenic potential in RUPP serum and decreased ($P<0.05$) endothelial tube formation in NP rats. RUPP rats presented with indices of oxidative stress such as increased placental catalase activity and plasma TBARS along with decreased plasma total antioxidant capacity compared to NP controls and pravastatin attenuated these effects. MAP, fetal weight, plasma VEGF, and plasma sFlt-1 were unchanged in NP+P compared to NP controls. The present data indicate that treatment with pravastatin attenuates oxidative stress and lowers MAP in placental ischemia-induced hypertension, but may have negative effects on circulating angiogenic potential during pregnancy. Further studies are needed to determine if there are long-term deleterious effects on maternal or fetal health following pravastatin treatment during pregnancy-induced hypertension or preeclampsia.

Endothelin-1, Oxidative Stress, and Endogenous Angiotensin II: Mechanisms of Angiotensin II Type I Receptor Autoantibody-Enhanced Renal and Blood Pressure Response During Pregnancy⁴

Abstract

Hypertension during preeclampsia is associated with increased maternal vascular sensitivity to angiotensin II (ANGII). This study was designed to determine mechanisms whereby agonistic autoantibodies to the ANGII type I receptor (AT1-AA) enhance blood pressure (MAP) and renal vascular sensitivity to ANGII during pregnancy. First, we examined MAP and renal artery resistance index (RARI) in response to chronic administration of ANGII or AT1-AA or AT1-AA+ANGII in pregnant rats compared to control pregnant rats. In order to examine mechanisms of heightened sensitivity in response to AT1-AA during pregnancy we examined the role of endogenous ANGII in AT1-AA infused pregnant rats, Endothelin-1 and oxidative stress in AT1-AA+ANGII treated rats. Chronic ANGII increased MAP from 95 \pm 2 in NP rats to 115 \pm 2 mmHg. Chronic AT1-AA increased MAP to 118 \pm 1 mmHg in NP rats which further increased to 123 \pm 2 with AT1-AA+ANGII. Increasing ANGII from (10-11-10-8) decreased Af-Art diameter 15–20% but sharply decreased Af-Art diameter 60% in AT1-AA pretreated vessels. RARI increased from 0.67 in NP rats to 0.70 with AT1-AA infusion, which was exacerbated to 0.74 in AT1-AA + ANGII infused rats. AT1-AA-induced hypertension decreased with Enalapril but was not attenuated. Both tissue ET-1 and ROS increased with AT1-AA+ANGII compared to AT1-AA alone and blockade of either of these pathways had significant effects on MAP or RARI. These data support the hypothesis that AT1-AA, via activation of ET-1 and oxidative stress and interaction with endogenous ANGII, are important mechanisms whereby MAP and renal vascular responses are enhanced during preeclampsia.

Urinary Excretion of c5b-9 in Severe Preeclampsia: Tipping the Balance of Complement Activation in Pregnancy⁵

Abstract

The complement cascade is activated in normal pregnancy and excessive complement activation propagates the systemic inflammatory response in severe preeclampsia. Consequently, biomarkers of complement dysregulation may be useful for prediction or treatment of disease. Since renal damage with proteinuria is a characteristic pathological feature of preeclampsia we hypothesized that complement markers in urine, rather than plasma, could better reflect complement dysregulation in disease. To investigate this we performed a case-control study of pregnant women, enrolling 25 cases of severe preeclampsia, 25 chronic hypertensive controls and 25 healthy non-hypertensive controls matched by gestational age and parity. Subjects were recruited from the Brigham and Women's Hospital from March 2012 through March 2013. Urine and blood samples were collected on the day of enrollment, with complement activation (C3a, C5a and C5b-9) measured by ELISA. Severe preeclampsia was associated with marked elevations in urinary C5b-9 [median ng/ml (IQ range) 4.3 (1.2–15.1)] relative to subjects with chronic hypertension 'Y (0-0)] and healthy controls 'Y (0-0)], $P<0.0001$. Urinary excretion of C5b-9 was detected in 96% of severe preeclamptics, 12% of chronic hypertensives and 8% of healthy controls. Cases were also notable for significantly greater urinary excretion of C3a and C5a. Plasma levels of C5a and C5b-9, but not C3a, were increased in severe preeclampsia compared to healthy controls; however, they did not distinguish preeclampsia from chronic hypertension, supporting our hypothesis that complement markers in urine rather than plasma better reflect complement dysregulation. Complement inhibition is an intriguing treatment option for patients with severe preeclampsia.

Preeclampsia Is Associated With the Presence of Transcriptionally Active Placental Fragments in the Maternal Lung⁶

Abstract

Preeclampsia is associated with increased levels of the circulating anti-angiogenic factor sFlt-1 and with an excessive shedding of placenta-derived multinucleated syncytial aggregates into the maternal circulation. However, it remains unclear whether these aggregates are transcriptionally active in the maternal organs and can therefore contribute to the systemic manifestations of preeclampsia. In this study, we measured placental sFlt-1 mRNA levels in preeclamptic and control placentas and performed RNA in situ hybridization to localize the main placental expression site of sFlt-1 mRNA. Because the maternal lung is the first capillary bed that circulating syncytial aggregates traverse, we studied the presence and persistence of placental material in lungs of preeclamptic and control subjects. To confirm the placental origin of these aggregates in maternal lungs, immunohistochemistry for the placenta-specific marker hCG and Y-chromosome in situ hybridization were performed. Using human placental tissue, we found that syncytial knots are the principal site of expression of the anti-angiogenic factor sFlt-1. In addition, autopsy material obtained from women with preeclampsia (n=9), showed significantly more placenta-derived syncytial aggregates in the lungs than in control subjects (n=26). Importantly, these aggregates still contained the anti-angiogenic factor sFlt-1 following their entrapment in the maternal lungs. The current study confirms the important role of syncytial knots in placental sFlt-1 mRNA production. Additionally, it shows a significant association between preeclampsia and larger quantities of sFlt-1 containing syncytial aggregates in maternal lungs, suggesting that the transfer of syncytial aggregates to the maternal compartment may contribute to the systemic endothelial dysfunction that characterizes preeclampsia.

Preterm Birth and Future Maternal Blood Pressure, Inflammation, and Intimal-Medial Thickness: The CARDIA Study⁷

Abstract

Preterm birth (PTB, <37 weeks) may be a marker of endothelial dysfunction and a proinflammatory phenotype; both are risk factors for cardiovascular disease. We studied 916 women (46% black) with 1181 live births between enrollment in the Coronary Artery Risk Development in Young Adults study (age 18–30 years) and 20 years later. C-reactive protein was measured at years 7, 15, and 20. Interleukin-6 and carotid intima-media thickness, which incorporated the common carotid arteries, bifurcations, and internal carotid arteries, were measured at year 20. Blood pressure, lipids, anthropometrics, and pregnancy events were assessed at all visits. Change in risk factors and differences in inflammatory markers and intima-media thickness according to PTB were evaluated. Women with PTBs (n=226) had higher mean systolic blood pressures before pregnancy (106 versus 105 mmHg, respectively; $P=0.03$). Systolic and diastolic blood pressure increased more rapidly over 20 years compared with women with term births ($P<0.01$ time interaction), even after removing women with self-reported hypertension in pregnancy. Women with PTB versus term births had similar mean intima-media thickness adjusted for age, body mass index, race, lifestyle, and cardiovascular risk factors. C-reactive protein and interleukin-6 did not differ according to PTB. Women with PTB, regardless of hypertension during pregnancy, had higher blood pressure after pregnancy compared with women with term births. In the United States, where rates of PTB are high and race disparities persist, PTB may identify women with higher blood pressure in the years after pregnancy.

Testosterone Alters Maternal Vascular Adaptations: Role of the Endothelial NO System⁸

Abstract

Sex steroid hormones estradiol and progesterone play an important role in vascular adaptations during pregnancy. However, little is known about the role of androgens. Plasma testosterone (T) levels are elevated in preeclampsia, mothers with polycystic ovary, and pregnant African American women, who have endothelial dysfunction and develop gestational hypertension. We tested whether increased T alters vascular adaptations during pregnancy and whether these alterations depend on endothelium-derived factors, such as prostacyclin, endothelium-derived hyperpolarizing factor, and NO. Pregnant Sprague Dawley rats were injected with vehicle (n=12) or T propionate [0.5 mg/Kg per day from gestation day 15–19; n=12] to increase plasma T levels 2-fold, similar to that observed in preeclampsia. Telemetric blood pressures and endothelium-dependent vascular reactivity were assessed with wire-myograph system. Phospho-endothelial NO synthase and total endothelial NO synthase were examined in mesenteric arteries. Mean arterial pressures were significantly higher starting from gestation day 19 until delivery in T-treated dams. Endothelium-dependent relaxation responses to acetylcholine were significantly lower in mesenteric arteries of T-treated dams (pD_2 [-log EC₅₀]=7.05±0.06; E_{max} =89.4±1.89) compared with controls (pD_2 =7.38±0.04; E_{max} =99.9±0.97). Further assessment of endothelial factors showed NO-mediated relaxations were blunted in T-treated mesenteric arteries (E_{max} =42.26±5.95) compared with controls (E_{max} =76.49±5.06); however, prostacyclin- and endothelium-derived hyperpolarizing factor-mediated relaxations were unaffected. Relaxation to sodium nitroprusside was unaffected with T-treatment. Phosphorylations of endothelial NO synthase at Ser1177 were decreased and at Thr495 increased in T-treated mesenteric arteries without changes in total endothelial NO synthase levels. In conclusion, increased maternal T, at concentrations relevant to abnormal clinical conditions, cause hypertension associated with blunting of NO-mediated vasodilation.

Administration of Interleukin-17 Soluble Receptor C Suppresses TH17 Cells, Oxidative Stress, and Hypertension in Response to Placental Ischemia During Pregnancy⁹

Abstract

Preeclampsia, new onset hypertension with proteinuria during pregnancy, is associated with chronic inflammation and placental oxidative stress (ROS). Chronic IL-17 increases blood pressure (MAP), autoantibodies (AT1-AA) and ROS during pregnancy. The objective of this study was to determine TH17 suppression via IL-17RC (recombinant receptor C) decreases pathophysiology associated with placental ischemia (RUPP). On gestation day 14, mini-osmotic pumps infusing 100 pg/day of IL-17RC were implanted into pregnant rats undergoing RUPP (Reduced Uterine Perfusion Pressure), gestation day 18 carotid catheters were inserted, day 19 MAP was recorded, TH17 cells, oxidative stress and AT1-AA were measured and analyzed via one-way ANOVA. MAP increased from 101 ± 2 mmHg in normal pregnant, NP (n=19), to 120 ± 1 mmHg in RUPP (n=17), but decreased to 110 ± 2 mmHg in RUPP+IL-17RC rats (n=22). Pup weight decreased from 2.28 ± 0.2 g in NP to 1.96 ± 0.3 g in RUPP rats, but was significantly increased to 2.1 in RUPP+IL-17RC rats. TH17 cells were 1.77% in RUPP but decreased to 0.65% in RUPP+IL-17RC rats. Urinary isoprostanes normalized in RUPP+IL-17RC rats (52 pg/μg) compared to 89 pg/μg in RUPP controls. Placental ROS was 652 RLU in RUPP, but decreased to 337 RLU in RUPP+IL-17RC rats. AT1-AA was 17.27 ± 0.7 bpm in RUPP but decreased to 5.00 ± 0.5 bpm in RUPP+IL-17RC rats. With this study, we show that infusion of IL-17RC blunts TH17s, oxidative stress, AT1-AA, and hypertension in the RUPP model of preeclampsia indicating that TH17 cells may play an important role in disease pathophysiology.

Podocyturia Predates Proteinuria and Clinical Features of Preeclampsia: Longitudinal Prospective Study¹⁰

Abstract

Podocyturia, the shedding of live podocytes, is present at delivery in women with preeclampsia. The aim of this study was to test whether podocyturia is present earlier in pregnancy and predicts for preeclampsia. We also aimed to compare test characteristics of podocyturia with those of angiogenic factors previously implicated in the pathogenesis of this disorder. We prospectively enrolled 315 women who provided blood and urine samples at the end of the second trimesters of their pregnancies (median, 27 gestational weeks) and within 24 hours of their deliveries (median, 39.5 gestational weeks). Blood samples were analyzed for angiogenic markers, including placental growth factor, the soluble receptor fms-like tyrosine kinase receptor-1 for vascular endothelial growth factor, and endoglin. The urine sediments were analyzed for podocytes, identified by staining for podocin after culturing the urinary sediments for 24 hours. This analysis included all women who developed preeclampsia (n=15), gestational hypertension (n=15), and a subsample of women who remained normotensive throughout pregnancy (n=44), matched for maternal age and number of previous pregnancies to those who developed preeclampsia. At the second trimester collection, all women who developed preeclampsia had podocyturia, compared with none of those who remained normotensive or were diagnosed with gestational hypertension. Podocyturia in the second trimester had a significantly greater sensitivity and specificity for the subsequent diagnosis of preeclampsia than any single angiogenic marker or a combination thereof. Screening for podocyturia at the end of the second trimester may allow for accurate identification of pregnant women at risk for preeclampsia.

Parental Smoking in Pregnancy and the Risks of Adult-Onset Hypertension¹¹

Abstract

Fetal exposure to parental smoking may lead to developmental adaptations and promote various diseases in later life. This study evaluated the associations of parental smoking during pregnancy with the risk of hypertension in the daughter in adulthood, and assessed whether these associations are explained by birth weight or body weight throughout life. We used data on 33086 participants of the Nurses' Health Study II and the Nurses' Mothers' Cohort. Cox proportional hazards models were used to examine the associations of maternal and paternal smoking during pregnancy with the nurse daughter, with self-reported physician-diagnosed hypertension from 1989 until 2007. Overall, 8575 (25.9%) mothers and 18874 (57.0%) fathers smoked during pregnancy. During follow-up, 7825 incident cases of adult-onset hypertension were reported. Both maternal and paternal smoking of ≥15 cigarettes/d during pregnancy were associated with increased risks of hypertension (rate ratio, 1.19; 95% CI, 1.09–1.29; and rate ratio, 1.18; 95% CI, 1.12–1.25, respectively) in the age-adjusted models. Further adjustment for birth weight did not affect the effect estimates appreciably, whereas additional adjustment for body shape and weight until age 18, or current body mass index, attenuated the associations with both maternal and paternal smoking (rate ratio, 1.07; 95% CI, 0.98–1.16; and rate ratio, 1.06; 95% CI, 1.01–1.12, respectively). The associations of parental smoking during pregnancy with the risk of hypertension in the offspring were largely explained by body weight throughout life, suggesting that these associations may not reflect direct intrauterine mechanisms.

Preeclampsia-Like Symptoms Induced in Mice by Fetoplacental Expression of STOX1 Are Reversed by Aspirin Treatment¹²

Abstract

Preeclampsia is a common human-specific pregnancy disorder defined by hypertension and proteinuria during gestation and responsible for maternal and fetal morbimortality. STOX1, encoding a transcription factor, was the first gene associated with preeclampsia as identified by positional cloning approaches. Its overexpression in choriocarcinoma cells mimics the transcriptional consequences of preeclampsia in the human placenta. Here, we created transgenic mouse strains overexpressing human STOX1. Wild-type female mice crossed with transgenic male mice reproduce accurately the symptoms of severe PE: gestational hypertension, proteinuria, and elevated plasma levels of soluble fms-like tyrosine kinase 1 and soluble endoglin. Placental and kidney histology were altered. Symptoms were prevented or alleviated by aspirin treatment. STOX1-overexpressing mice constitute a unique model for studying preeclampsia, allow testing therapeutic approaches, and assessing the long-term effects of the preeclamptic syndrome.

Hypertensive Disorders of Pregnancy and Cardiometabolic Health in Adolescent Offspring¹³

Abstract

An accumulating body of evidence suggests that offspring of mothers with preeclampsia have higher blood pressure during childhood and young adulthood compared with women without preeclampsia. However, the evidence with regard to offspring glucose metabolism and lipids is more scant. We examined whether maternal hypertensive disorders of pregnancy (preeclampsia and gestational hypertension) are associated with a range of cardiometabolic health measures in adolescent offspring. We included data for mother-offspring pairs from a United Kingdom prospective birth cohort (the Avon Longitudinal Study of Parents and Children). Repeat antenatal clinic measures of blood pressure and proteinuria (median 14 and 11, respectively) were used to ascertain maternal preeclampsia (n=53) and gestational hypertension (n=431). Offspring had blood pressure (n=4438), and fasting lipids, insulin, and glucose (n=2888) measured at a mean age of 17 years. There was no strong evidence of differences in fasting insulin, glucose, or lipid concentrations. Systolic and diastolic blood pressures were higher in offspring of mothers with gestational hypertension (mean difference, 2.06 mm Hg; 95% confidence interval, 1.28–2.84 and 1.11 mm Hg; 95% confidence interval, 0.54–1.69, respectively) and preeclampsia (1.12 mm Hg; 95% confidence interval, –0.89–3.12 and 1.71 mm Hg; 95% confidence interval, 0.23–3.17, respectively) compared with offspring of mothers without hypertensive disorders of pregnancy, adjusting for potential confounders (age, sex, maternal age at delivery, household social class, prepregnancy body mass index, parity, and smoking in pregnancy). Results suggest a specific association between maternal hypertensive disorders of pregnancy and offspring blood pressure that may be driven by genetics or familial nongenetic risk factors particular to blood pressure.

MicroRNA-376c Impairs Transforming Growth Factor-Beta and Nodal Signaling to Promote Trophoblast Cell Proliferation and Invasion¹⁴

Abstract

Preeclampsia is a major disorder of pregnancy and a leading cause of maternal and perinatal morbidity and mortality. MicroRNAs are small noncoding RNAs that regulate gene expression posttranscriptionally. In this study, we examined the expression of miR-376c and found that miR-376c levels were downregulated in both placental and plasma samples collected from preeclamptic patients, when compared with the normal pregnant women at the same gestational stage. Overexpression of miR-376c induced trophoblast cell proliferation, migration, and invasion in HTR8/SVneo cells and promoted placental explant outgrowth. In contrast, inhibition of endogenous miR-376c resulted in a decrease in trophoblast cell invasion and placental explant outgrowth. We identified activin receptor-like kinase 5 (ALK5), a type I receptor for transforming growth factor- β , and ALK7, a type I receptor for Nodal, as targets of miR-376c. Overexpression of miR-376c repressed transforming growth factor- β and Nodal functions, whereas overexpression of ALK5 and ALK7 reversed the effects of miR-376c. These results demonstrate that miR-376c inhibits both ALK5 and ALK7 expression to impair transforming growth factor- β /Nodal signaling, leading to increases in cell proliferation and invasion. An unbalanced Nodal/transforming growth factor- β and miR-376c expression may lead to the development of preeclampsia.

Maternal Prepregnancy Body Mass Index and Their Children's Blood Pressure and Resting Cardiac Autonomic Balance at Age 5 to 6 Years¹⁵

Abstract

Adverse intrauterine conditions can program hypertension. Because one of the underlying mechanisms is thought to be cardiac autonomic balance, we investigated the association between pre-pregnancy body mass index (BMI) and blood pressure and indicators of the autonomic balance in the child at age 5–6 years. Also investigated was whether these associations were mediated by standardized birth weight and child BMI. Pregnant women (n=3074) participating in the ABCD study completed a questionnaire at gestational week 14. At age 5–6 years, offspring's sympathetic drive (pre-ejection period), parasympathetic drive (respiratory sinus arrhythmia) and heart rate were measured by electrocardiography and impedance cardiography at rest. Blood pressure was assessed simultaneously. After adjusting for possible maternal/offspring confounders, pre-pregnancy BMI was positively linearly associated with diastolic blood pressure (β :0.11 mmHg, 95% confidence interval [CI], 0.05–0.17), systolic blood pressure (β :0.14 mmHg, 95% CI, 0.07–0.21), but not with heart rate, sympathetic or parasympathetic drive. After adding birth weight and child BMI to the model, the independent effect size of pBMI on SBP (β :0.07 mmHg, 95% CI, 0.00–0.14) and DBP (β :0.07 mmHg, 95% CI, 0.01–0.13) decreased by about 50%. Birth weight did not mediate these relationships, but was independently and negatively associated with blood pressure. Child BMI was positively associated with blood pressure and partly mediated the association between pre-pregnancy BMI and blood pressure. In conclusion, higher pre-pregnancy BMI is associated with higher blood pressure in the child (aged 5–6 years) but does not seem to be due to early alterations in resting cardiac autonomic balance. Child BMI, but not birth weight, mediated the association between pre-pregnancy BMI and blood pressure.

Cellular Fetal Microchimerism in Preeclampsia¹⁶

Abstract

Previous studies have shown elevated concentrations of free fetal DNA and erythroblasts in maternal circulation in women with preeclampsia compared with those with normal pregnancy. Pluripotent and immunocompetent fetal cells also transfer to the maternal circulation during pregnancy, but whether concentrations of fetal mononuclear cells also differed in preeclampsia was unknown. We sought to quantify cellular fetal microchimerism in maternal circulation in women with preeclampsia and healthy controls. We studied women with preeclampsia and compared them with women with healthy pregnancies at similar gestational age. To identify a targetable polymorphism unique to the fetus to quantify fetal microchimerism, participants and family members were genotyped for the human leukocyte antigen loci DRB1, DQA1, and DQB1, as well as several other polymorphisms. A panel of polymorphism-specific quantitative polymerase chain reaction assays was used to identify and quantify fetal microchimerism in maternal peripheral blood mononuclear cells. Of 53 preeclampsia samples tested for cellular fetal microchimerism, 17 (32%) were positive when compared with 6 of 57 (6%) control samples (unadjusted odds ratio for detection, 4.0; 95% confidence interval, 1.5–11.1; $P=0.007$). The concentration of cellular fetal microchimerism (expressed as genome equivalents of fetal microchimerism per 100 000 maternal genome equivalents) was also higher among women with preeclampsia: median 0.0, mean 5.7, range 0 to 153.7, compared with those with controls: median 0.0, mean 0.3, range 0 to 9.1, $P=0.002$. We conclude that women with preeclampsia harbor cellular fetal microchimerism more commonly and at higher concentrations compared with women with uncomplicated pregnancy. The functional capacity and phenotype of these fetal cells are not yet known.

Novel Role of the Renin-Angiotensin System in Preeclampsia Superimposed on Chronic Hypertension and the Effects of Exercise in a Mouse Model¹⁷

Abstract

Gestational hypertensive disorders, such as preeclampsia, affect 6% to 8% of all pregnancies in North America, and they are the leading cause of maternal mortality in industrialized countries, accounting for 16% of deaths. Women with hypertension have an increased risk (15% to 25%) of developing preeclampsia. Our aim was to investigate the mechanisms implicated in preeclampsia superimposed on chronic hypertension and in the protective effects of exercise in a mouse model. Female mice overexpressing human angiotensinogen and human renin were used as a model of preeclampsia superimposed on chronic hypertension. In the trained group, mothers were placed in cages with access to a wheel before mating, and they remained within these throughout gestation. Blood pressure was measured by telemetry. We found that angiotensin II type I receptor was increased, whereas the Mas receptor was decreased in the placenta and the aorta of pregnant sedentary transgenic mice. This would produce a decrease in angiotensin-(1–7) effects in favor of angiotensin II. Supporting the functional contribution of this modulation, we found that the prevention of most pathological features in trained transgenic mice was associated with a normalization of placental angiotensin II type 1 and Mas receptors and an increase in aortic Mas receptor. We also found reduced circulating and placental soluble Fms-like tyrosine kinase-1 in trained transgenic mice compared with sedentary mice. This study demonstrates that modulation of the renin–angiotensin system is a key mechanism in the development of preeclampsia superimposed on chronic hypertension, which can be altered by exercise training to prevent disease features in an animal model.

Vascular Endothelial Growth Factor-A and Aldosterone: Relevance to Normal Pregnancy and Preeclampsia¹⁸

Abstract

Aldosterone levels are markedly elevated during normal pregnancy but fall even though volume contracts when preeclampsia occurs. The level of aldosterone in either condition cannot be explained solely by the activity of the renin-angiotensin II system. In normal gestation, vascular endothelial growth factor (VEGF) is thought to maintain vascular health, but its role in adrenal hormone production is unknown. We hypothesized that the role of VEGF in the adrenal gland is to maintain vascular health and regulate aldosterone production. Here, we demonstrate that supernatant of endothelial cells grown in the presence of VEGF enhanced aldosterone synthase activity in human adrenocortical cells. VEGF either alone or combined with angiotensin II increased aldosterone production in adrenal cells. These data suggest that endothelial cell-dependent and independent activation of aldosterone is regulated by VEGF. In contrast to angiotensin II, VEGF did not upregulate the steroidogenic acute regulatory protein. Consistent with this observation, angiotensin II stimulated both aldosterone and cortisol synthesis from progesterone, whereas VEGF stimulated selectively aldosterone production. In rats, overexpression of soluble fms-like tyrosine kinase-1, an endogenous VEGF inhibitor, led to adrenocortical capillary rarefaction and fall in aldosterone concentrations that correlated inversely with soluble fms-like tyrosine kinase-1 levels. These findings may explain why aldosterone increases so markedly during normal gestation and why preeclampsia, a condition characterized by high soluble fms-like tyrosine kinase-1, is associated with inappropriately low aldosterone levels in spite of relatively lower plasma volumes.

Hypertension After Preeclampsia Is Preceded by Changes in Cardiac Structure and Function¹⁹

Abstract

Preeclampsia is associated with a 4-fold higher risk for developing remote chronic hypertension. Preeclampsia is accompanied by left ventricular hypertrophy and decreased diastolic function, which may or may not resolve postpartum. We tested the hypothesis that increased measures of cardiac geometry and decreased cardiac function persisting for ≥ 6 months postpartum in normotensive women with a history of preeclampsia precede the development of later chronic hypertension. Formerly preeclamptic women ($n=652$) underwent echocardiography at 9 months (range, 6–19) postpartum. We excluded women with preexisting hypertension ($n=42$), hypertension at the postpartum screening ($n=133$), and those that did not return any checklist ($n=128$). Eventually, 349 women were included. Remote health was evaluated by a biennially checklist. We used Cox regression for analysis. Twenty-seven (8%) normotensive women had developed chronic hypertension during a medium follow-up period of 6 years. At screening they differed from their counterparts who remained normotensive by hazard ratio for left ventricular mass index (1.11; 95% confidence interval [CI], 1.03–1.18), diastolic blood pressure (1.13; 95% CI, 1.06–1.20), systolic blood pressure (1.07; 95% CI, 1.02–1.11), mean arterial pressure (1.11; 95% CI, 1.05–1.18), heart rate (1.05; 95% CI, 1.01–1.10), and E/A ratio (0.22; 95% CI, 0.06–0.85). Backward stepwise analysis showed independent hazard ratio for left ventricular mass index and diastolic blood pressure 1.08 (95% CI, 1.01–1.16) and 1.13 (95% CI, 1.06–1.21), respectively. In conclusion, the development of later chronic hypertension in initially normotensive formerly preeclamptic women is preceded by increased left ventricular mass index and diastolic blood pressure at postpartum screening.

Renal Denervation Abolishes the Age-Dependent Increase in Blood Pressure in Female Intrauterine Growth-Restricted Rats at 12 Months of Age²⁰

Abstract

Perinatal insults program sex differences in blood pressure, with males more susceptible than females. Aging may augment developmental programming of chronic disease, but the mechanisms involved are not clear. We previously reported that female growth-restricted offspring are normotensive after puberty. Therefore, we tested the hypothesis that age increases susceptibility to hypertension in female growth-restricted offspring. Blood pressure remained similar at 6 months of age; however, blood pressure was significantly elevated in female growth-restricted offspring relative to control by 12 months of age (137 ± 3 vs 117 ± 4 mmHg; $P<0.01$, respectively). Body weight did not differ at 6 or 12 months of age; however, total fat mass and visceral fat were significantly increased at 12 months in female growth-restricted offspring ($P<0.05$ vs control). Glomerular filtration rate remained normal, yet renal vascular resistance was increased at 12 months of age in female growth-restricted offspring ($P<0.05$ vs control). Plasma leptin, which can increase sympathetic nerve activity, did not differ at 6 months but was increased at 12 months of age in female growth-restricted offspring ($P<0.05$ vs control). Because of the age-dependent increase in leptin, we hypothesized that the renal nerves may contribute to the age-dependent increase in blood pressure. Bilateral renal denervation abolished the elevated blood pressure in female growth-restricted offspring normalizing it relative to denervated female control offspring. Thus, these data indicate that age induces an increase in visceral fat and circulating leptin associated with a significant increase in blood pressure in female growth-restricted offspring, with the renal nerves serving as an underlying mechanism.

Dynamic Cerebral Autoregulation in Pregnancy and the Risk of Preeclampsia²¹

Abstract

Preeclampsia may affect severely the cerebral circulation leading to impairment of cerebral autoregulation, edema, and ischemia. It is not known whether impaired autoregulation occurs before the clinical onset of preeclampsia, and whether this can predict the occurrence of preeclampsia. Seventy-two women at 25 to 28 weeks of gestation were studied. Control values were derived from 26 nonpregnant women. Dynamic properties of cerebral autoregulation (DCA) were measured in the middle and posterior cerebral artery using transcranial Doppler and transfer function analysis (phase and gain) of respiratory-induced 0.1 Hz hemodynamic oscillations. Uterine artery ultrasound was performed to search for a notch sign as an early marker of general endothelial dysfunction. All women were followed up until 6 weeks after delivery for the occurrence of preeclampsia. The autoregulation parameter gain did not differ between pregnant and nonpregnant women. Phase was slightly but significantly higher in pregnant women, indicating better DCA. Women with a notch sign did not show altered DCA. A history of preeclampsia during a previous pregnancy was associated with lower phase in middle cerebral artery and posterior cerebral artery ($P < 0.05$ each). During follow-up, 9 women developed preeclampsia. None of the DCA parameters were associated with the occurrence of preeclampsia. In conclusion, DCA is well preserved during late midterm pregnancy, even in women with disturbed uterine blood flow. Yet, pregnant women with preeclampsia in a previous pregnancy seem to have poorer DCA. Although limited in statistical power, this study does not support DCA as a strong early risk marker of preeclampsia.

Estradiol-17 β and Its Cytochrome P450- and Catechol-O-Methyltransferase-Derived Metabolites Stimulate Proliferation in Uterine Artery Endothelial Cells: Role of Estrogen Receptor- α Versus Estrogen Receptor- β ²²

Abstract

Estradiol-17 β (E2 β) and its metabolites, which are sequentially synthesized by cytochrome P450s and catechol-O-methyltransferase to form 2 and 4-hydroxyestradiol (OHE2) and 2- and 4-methoxyestradiol (ME2), are elevated during pregnancy. We investigated whether cytochrome P450s and catechol-O-methyltransferase are expressed in uterine artery endothelial cells (UAECs) and whether E2 β and its metabolites modulate cell proliferation via ER- α and/or ER- β and play roles in physiological uterine angiogenesis during pregnancy. Cultured ovine UAECs from pregnant and nonpregnant ewes were treated with 0.1 to 100.0 nmol/L of E2 β , 2-OHE2, 4-OHE2, 2-ME2, and 4-ME2. ER- α or ER- β specificity was tested using ICI 182 780, ER- α -specific 1,3-bis(4-hydroxyphenyl)-4-methyl-5-[4-(2-piperidinylethoxy)phenol]-1H-pyrazole dihydrochloride, ER- β -specific 4-[2-phenyl-5,7-bis(trifluoromethyl)pyrazolo [1,5-a]pyrimidin-3-yl]phenol antagonists and their respective agonists ER- α -specific 4,4',4''-(4-propyl-[1H]-pyrazole-1,3,5-triyl)trisphenol and ER- β -specific 2,3-bis(4-Hydroxyphenyl)-propionitrile. Angiogenesis was evaluated using 5-bromodeoxyuridine proliferation assay. Using confocal microscopy and Western analyses to determine enzyme location and levels, we observed CYP1A1, CYP1A2, CYP1B1, CYP3A4, and catechol-O-methyltransferase expression in UAECs; however, expressions were similar between nonpregnant UAECs and pregnant UAECs. E2 β , 2-OHE2, 4-OHE2, and 4-ME2 treatments concentration-dependently stimulated proliferation in pregnant UAECs but not in nonpregnant UAECs; 2-ME2 did not stimulate proliferation in either cell type. Proliferative responses of pregnant UAECs to E2 β were solely mediated by ER- β , whereas responses

to E2 β metabolites were neither ER- α nor ER- β mediated. We demonstrate an important vascular role for E2 β , its cytochrome P450- and catechol-O-methyltransferase-derived metabolites, and ER- β in uterine angiogenesis regulation during pregnancy that may be dysfunctional in preeclampsia and other cardiovascular disorders.

Aberrant Synthesis, Metabolism, and Plasma Accumulation of Circulating Estrogens and Estrogen Metabolites in Preeclampsia Implications for Vascular Dysfunction²³

Abstract

Estrogens and estrogen metabolites have important functions in cardiovascular and other physiology, yet the patterns of estrogen synthesis, metabolism, and the individual plasma profile of estrogens and estrogen metabolites during human pregnancy as well as in preeclampsia remain undetermined. We performed liquid chromatography mass spectrometry on plasma samples from normotensive pregnant women (normP; n=8), women with mild (mPE; n=8), and severe (sPE; n = 8) preeclampsia at labor. Compared with normP, estrone was lower in sPE, whereas plasma level of estradiol-17 β was significantly lower in women with mPE and sPE. Estriol was lower in sPE, but not in mPE. Although 2-hydroxyestrone was lower in mPE and sPE, 4-hydroxyestrone was high in sPE. 16- α -hydroxyestrone was higher in mPE, but not in sPE. 2-hydroxyestradiol in women with mPE and sPE were lower compared with normP. Compared with 2-methoxyestrone in normP, levels were lower in sPE. 3-methoxyestrone and 4-methoxyestrone were unchanged. 2-methoxyestradiol was lower in mPE and sPE; however, 4-methoxyestradiol was low only in sPE. Compared with normP, 16-keto-estradiol-17 β levels were significantly higher in sPE, whereas 16-epi-estriol and 17-epi-estriol were lower in women with sPE. Our findings show that preeclampsia is characterized by aberrant synthesis, metabolism, and accumulation of estrogens and estrogen metabolites that are likely to be associated with alterations in vascular function. These results underscore the need to investigate the functional vascular and other physiology of estrogens and estrogen metabolites in the pathophysiology of preeclampsia.

Endothelial NO Synthase Augments Fetoplacental Blood Flow, Placental Vascularization, and Fetal Growth in Mice²⁴

Abstract

It is not known whether eNOS deficiency in the mother or the conceptus (ie, placenta and fetus) causes fetal growth restriction in mice lacking the endothelial NO synthase gene (eNOS knockout [KO]). We hypothesized that eNOS sustains fetal growth by maintaining low fetoplacental vascular tone and promoting fetoplacental vascularity and that this is a conceptus effect and is independent of maternal genotype. We found that eNOS deficiency blunted fetal growth, and blunted the normal increase in umbilical blood flow and umbilical venous diameter and the decrease in umbilical arterial Resistance Index in late gestation (14.5–17.5 days) in eNOS KO relative to C57Bl/6J controls. On day 17.5, fetoplacental capillary lobule length and capillary density in vascular corrosion casts were reduced in eNOS KO placentas. Reduced vascularization may be a result of decreased vascular endothelial growth factor mRNA and protein expression in eNOS KO placentas at this stage. These factors, combined with significant anemia found in eNOS KO fetuses, would be anticipated to reduce fetal oxygen delivery and contribute to the fetal tissue hypoxia that was detected in the heart, lung, kidney, and liver by immunohistochemistry using pimonidazole. Although maternal eNOS deficiency impairs uteroplacental adaptations to pregnancy, maternal genotype was not a significant factor affecting growth in heterozygous conceptuses. This indicates that fetal growth restriction was primarily caused by conceptus eNOS deficiency. In mice, placental hemodynamic and vascular changes with gestation and growth restriction showed strong parallels with human pregnancy. Thus, the eNOS KO model could provide insights into the pathogenesis of human intrauterine growth restriction.

Single Nucleotide Polymorphisms in G Protein Signaling Pathway Genes in Preeclampsia²⁵

Abstract

Preeclampsia is a pregnancy specific disorder and a risk factor for later cardiovascular disease. The cause and detailed pathophysiology remains unknown. G protein signaling is involved in a variety of physiological processes, including blood pressure regulation. We assessed whether distributions of 3 single nucleotide polymorphisms in genes coding for components of G protein signaling pathways that have been associated with hypertension differ between women with preeclampsia and normotensive pregnant women; the G protein $\beta 3$ subunit gene (GNB3) C825T polymorphism (rs5443), the angiotensin II type 1 receptor gene (AGTR1) 3'UTR A1166C polymorphism (rs5186), and the regulator of G protein signaling 2 gene (RGS2) 3'UTR C1114G polymorphism (rs4606). Two separate Norwegian study populations were used; a large population based study and a smaller, but clinically well-described pregnancy biobank. A descriptive study of 43 women with eclampsia was additionally included. In the population-based study, an increased odds of preeclampsia (odds ratio, 1.21; [95% confidence interval, 1.05–1.40]; $P=0.009$) and recurrent preeclampsia (odds ratio, 1.43; [95% confidence interval, 1.06–1.92]; $P=0.017$) was found in women carrying the rs4606 CG or GG genotype. In early-onset preeclamptic patients with decidual spiral artery biopsies available (n=24), the rs4606 CG or GG genotype was more frequent in those with acute atherosclerosis (resembling early stage of atherosclerosis) compared with those without: odds ratio, 15.0; (95% confidence interval, 2.02–111.2); $P=0.004$. No association was found between preeclampsia and the rs5443 or the rs5186. The genotype distribution in eclamptic women was not different from preeclamptic women. In conclusion, RGS2 rs4606 may affect the risk and progression of preeclampsia.

Psychosocial Stress Related to the Loss of a Close Relative the Year Before or During Pregnancy and Risk of Preeclampsia²⁶

Abstract

The role of stress in the pathogenesis of preeclampsia has only been investigated in a few studies, and the findings are not conclusive. We analyzed whether maternal bereavement shortly before or during pregnancy is associated with an increased risk of preeclampsia. We conducted a cohort study of singleton births in Denmark during 1978–2008 and in Sweden during 1973–2006 (n=4 122 490) by linking national population-based registers. Mothers were considered exposed to bereavement if they lost a parent, a sibling, a partner, or a child the year before or during pregnancy (n=124 553). The risk of preeclampsia was slightly increased for women who lost a close relative during the 6 months before conception (odds ratio [OR], 1.14; 95% confidence interval [CI], 1.06–1.23) or during the first trimester of pregnancy (OR, 1.15; 95% CI, 1.03–1.29). Exposure during these periods tended to be more closely related to early preeclampsia (delivery before 34 weeks of gestation; OR, 1.37; 95% CI, 1.12–1.67) than to late preeclampsia (OR, 1.13; 95% CI, 1.06–1.20). The strongest association was observed between loss of a child and early preeclampsia when the exposure window was from 6 months before pregnancy until start of second trimester (OR, 4.03; 95% CI, 2.46–6.61). Our results related to timing of exposure suggest that severe stress may influence early placentation. However, the public health implications of our findings are limited in populations with a low prevalence of severe stress exposures.

Circulating Angiogenic Factors and Urinary Prolactin as Predictors of Adverse Outcomes in Women With Preeclampsia²⁷

Abstract

Preeclampsia is characterized by an imbalance in angiogenic factors. Urinary prolactin (PRL) levels and its antiangiogenic PRL fragments have been associated with disease severity. In this study, we assessed whether these biomarkers are associated with an increased risk of adverse maternal and perinatal outcomes in preeclamptic women. We studied 501 women with preeclampsia attended at a tertiary care hospital. Serum concentrations of soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), and soluble endoglin (sEng), as well as urinary PRL levels, were measured by enzyme-linked immunosorbent assay. Antiangiogenic PRL fragments were determined by immunoblotting. The risk for any adverse maternal outcome and for having a small-for-gestational-age infant was higher among women with sFlt-1/PlGF ratios, sEng, and urinary PRL level values in the highest quartile (odds ratios ≥ 2.7), compared with the lowest quartile. Both urinary PRL levels and the presence of antiangiogenic PRL fragments were more closely associated with the risk of specific adverse maternal outcomes (placental abruption, hepatic hematoma or rupture, acute renal failure, pulmonary edema, maternal death, and need for endotracheal intubation, positive inotropic drug support, and hemodialysis; odds ratios ≥ 5.7 and ≥ 4.7 , respectively) than either sFlt-1/PlGF ratio or sEng alone. We concluded that in preeclamptic women at the time of initial evaluation, sFlt-1/PlGF ratio and sEng are associated with increased risk of combined adverse maternal outcomes. However, urinary PRL concentrations and its antiangiogenic fragments appear to be better predictors of an adverse maternal outcome and may be useful for risk stratification in preeclampsia.

Folic Acid Supplementation During Early Pregnancy and the Risk of Gestational Hypertension and Preeclampsia²⁸

Abstract

Emerging evidence has suggested that folic acid-containing multivitamins may markedly reduce the risk of gestational hypertension or preeclampsia. We examined whether maternal supplementation with folic acid alone during early pregnancy can prevent the occurrence of gestational hypertension and preeclampsia. The data are from a large population-based cohort study established to evaluate the effectiveness of the campaign to prevent neural tube defects with folic acid supplementation in China. We selected participants who were registered in 2 southern provinces, had exact information on folic acid use, and were not affected by chronic hypertension or diabetes mellitus before 20 weeks gestation. A logistic regression model was used to adjust for the effects of the main potential confounders, including age, body mass index, education, occupation, parity, and multiple births. The study size had 99.9% power ($\alpha=0.05$) to detect a decrease of 10% over the unexposed rate of 9.4% for gestational hypertension. Among the 193 554 women (47.9% took folic acid, 52.1% did not), the overall incidence of gestational hypertension and preeclampsia was 9.5% and 2.5%, respectively. The incidence of gestational hypertension and preeclampsia was 9.7% and 2.5% for women who took folic acid, and 9.4% and 2.4% for women who did not use it. The adjusted risk ratio associated with folic acid use was 1.08 (95% confidence interval, 1.04–1.11) for gestational hypertension and 1.11 (95% confidence interval, 1.04–1.18) for preeclampsia. Our findings suggest that daily consumption of 400 μg folic acid alone during early pregnancy cannot prevent the occurrence of gestational hypertension and preeclampsia.

Changes in Retinal Microvascular Caliber Precede the Clinical Onset of Preeclampsia²⁹

Abstract

Preeclampsia is a leading cause of maternal morbidity and mortality. The degree of maternal cardiovascular dysfunction that precedes the onset of preeclampsia is largely unknown. This prospective cohort study aimed to characterize differences in vivo in retinal microvascular caliber and blood pressure throughout pregnancy in relation to preeclampsia development. Women were recruited from Royal Prince Alfred Hospital, Sydney, Australia, of which 92 women were included in the study. Retinal images and blood pressures were collected at 13, 19, 29, and 38 weeks of gestation. Retinal vessels were analyzed as the central retinal arteriolar equivalent corrected for mean arterial blood pressure and the central retinal venular equivalent corrected for mean arterial blood pressure, using generalized linear models adjusted for age and body mass index. The preeclampsia group were significantly older ($P=0.002$) and had a significantly higher mean body mass index ($P=0.005$). The central retinal arteriolar equivalent corrected for mean arterial blood pressure was significantly reduced at 13 ($P=0.03$), 19 ($P=0.007$), and 38 ($P=0.03$) weeks of gestation in the preeclampsia group. The central retinal venular equivalent corrected for mean arterial blood pressure was also significantly lower at 13 ($P=0.04$) and 19 ($P=0.001$) weeks of gestation in the women who progressed to preeclampsia. This study directly documents increased peripheral resistance in vivo, observed as the combination of constricted retinal arterioles or venules and elevated blood pressure, in women who later developed preeclampsia. This difference preceded the clinical signs of preeclampsia.

Temporal Changes in Retinal Microvascular Caliber and Blood Pressure During Pregnancy³⁰

Abstract

The microvasculature plays an important role in regulating cardiovascular changes in pregnancy, but changes in microvasculature have been difficult to document in vivo. This study objectively quantifies changes in the maternal retinal arteriolar and venular caliber over the course of healthy pregnancy. Healthy pregnant women ($n=53$) were recruited from Royal Prince Alfred Hospital, Sydney, Australia. Retinal images and mean arterial blood pressures (MAP) were collected at 13, 19, 29, and 38 weeks of gestation and at 6-month postpartum. Retinal vessels were analyzed and summarized as the central retinal arteriolar equivalent and central retinal venular equivalent. Central retinal arteriolar equivalent and central retinal venular equivalent were corrected for MAP. Paired *t* tests were performed comparing consecutive time points, with a significance level of $P<0.01$. There was a decrease in MAP between 13- and 19-week gestation ($P=0.001$) followed by a return to baseline from 19 weeks to delivery. This was correlated by an increase in vessel caliber between 13- and 19-week gestation (central retinal arteriolar equivalent: $P<0.001$, central retinal venular equivalent: $P=0.007$) and a return to baseline from 19 weeks to delivery. There were no differences in the central retinal arteriolar equivalent or central retinal venular equivalent (both uncorrected and corrected for MAP) between nulliparous and parous women. The pattern of dilatation and constriction in the microvasculature mirrored the changes in MAP throughout pregnancy, reflecting changes in peripheral resistance. This study provides insights into physiological changes in the microvasculature throughout a healthy pregnancy. These results can be used as a baseline with which to compare the changes observed in pathological conditions of pregnancy.

Spiral Artery Remodeling and Trophoblast Invasion in Preeclampsia and Fetal Growth Restriction: Relationship to Clinical Outcome³¹

Abstract

Failure to transform uteroplacental spiral arteries is thought to underpin disorders of pregnancy, including preeclampsia and fetal growth restriction (FGR). In this study, spiral artery remodeling and extravillous-cytotrophoblast were examined in placental bed biopsies from normal pregnancy ($n=25$), preeclampsia ($n=22$), and severe FGR ($n=10$) and then compared with clinical parameters. Biopsies were immunostained to determine vessel wall integrity, extravillous-cytotrophoblast location/density, periarterial fibrinoid, and endothelium. Muscle disruption was reduced in myometrial spiral arteries in preeclampsia ($P=0.0001$) and FGR ($P=0.0001$) compared with controls. Myometrial vessels from cases with birth weight <5th percentile ($P<0.001$), abnormal uterine Doppler ($P<0.01$), abnormal umbilical artery Doppler ($P<0.001$), and preterm delivery ($P<0.001$) had less muscle destruction compared with >5th percentile. Fewer extravillous-cytotrophoblast surrounded both decidual and myometrial vessels in the normal group and preeclampsia group compared with the FGR group ($P=0.001$). For myometrial vessels, the normal group contained more intramural extravillous-cytotrophoblast than in preeclampsia ($P=0.015$). Decidual vessels in the FGR group had less fibrinoid deposition compared with controls ($P=0.013$). For myometrial vessels, less fibrinoid was deposited in both the preeclampsia group ($P=0.0001$) and the FGR group ($P=0.01$) when compared with controls, and less fibrinoid was deposited in the preeclampsia group when compared with FGR group ($P<0.001$). Myometrial vessels obtained from birth weights <5th percentile had less periarterial fibrinoid than those with >5th percentile ($P<0.02$). A major defect in myometrial spiral artery remodeling occurs in preeclampsia and FGR that is linked to clinical parameters. Interstitial extravillous-cytotrophoblast is not reduced in preeclampsia but is increased in FGR.

Increased Salt Sensitivity of Ambulatory Blood Pressure in Women With a History of Severe Preeclampsia³²

Abstract

Cardiovascular diseases are the principal cause of death in women in developed countries and are importantly promoted by hypertension. The salt sensitivity of blood pressure (BP) is considered as an important cardiovascular risk factor at any BP level. Preeclampsia is a hypertensive disorder of pregnancy that arises as a risk factor for cardiovascular diseases. This study measured the salt sensitivity of BP in women with a severe preeclampsia compared with women with no pregnancy hypertensive complications. Forty premenopausal women were recruited 10 years after delivery in a case-control study. Salt sensitivity was defined as an increase of >4 mmHg in 24-hour ambulatory BP on a high-sodium diet. The ambulatory BP response to salt was significantly increased in women with a history of preeclampsia compared with that of controls. The mean (95% confidence interval) daytime systolic/diastolic BP increased significantly from 115 (109–118)/79 (76–82) mmHg on low-salt diet to 123 (116–130)/80 (76–84) on a high-salt diet in women with preeclampsia, but not in the control group (from 111 [104–119]/77 [72–82] to 111 [106–116]/75 [72–79], respectively, $P<0.05$). The sodium sensitivity index ($SSI = \Delta \text{mean arterial pressure} / \Delta \text{urinary Na excretion} \times 1000$) was 51.2 (19.1–66.2) in women with preeclampsia and 6.6 (5.8–18.1) mmHg/mol per day in controls ($P=0.015$). The nocturnal dip was blunted on a high-salt diet in women with preeclampsia. Our study shows that women who have developed preeclampsia are salt sensitive before their menopause, a finding that may contribute to their increased cardiovascular risk. Women with a history of severe preeclampsia should be targeted at an early stage for preventive measures of cardiovascular diseases.

Prenatal Programming of Hypertension Induces Sympathetic Overactivity in Response to Physical Stress³³

Abstract

Small-for-gestational-age infants are known to develop hypertension in adulthood. This prenatal programming of hypertension (PPH) can result from several insults including maternal dietary protein deprivation, uteroplacental insufficiency, and prenatal administration of glucocorticoids. The mechanisms underlying the development of hypertension remain unclear although the sympathetic nervous system has been indirectly implicated. This study was designed to directly measure renal sympathetic nerve activity both at rest and during physical stress in an animal model of PPH. The adult male offspring of rats fed either a 6% (PPH) or 20% protein diet (control) were investigated. Conscious systolic blood pressure measured by tail cuff was significantly higher in PPH compared with control (140 ± 3 versus 128 ± 3 mmHg; $P<0.05$). Baseline mean arterial pressure, heart rate, and renal sympathetic activity were not different between groups during isoflurane anesthesia or after decerebration. Physical stress was induced in decerebrate animals by activating the exercise pressor reflex during static muscle contraction. Stimulation of the exercise pressor reflex evoked significantly larger changes from baseline in mean arterial pressure (40 ± 7 versus 20 ± 4 mmHg; $P<0.05$), heart rate (19 ± 3 versus 5 ± 1 bpm; $P<0.05$), and renal sympathetic activity ($198 \pm 29\%$ versus $68 \pm 14\%$; $P<0.05$) in PPH as compared with control. The data demonstrate that the sympathetic response to physical stress is markedly exaggerated in PPH and may play a significant role in the development of hypertension in adults born small for gestational age.

Integrated Proteomics Pipeline Yields Novel Biomarkers for Predicting Preeclampsia³⁴

Abstract

Preeclampsia, a hypertensive pregnancy complication, is largely unpredictable in healthy nulliparous pregnant women. Accurate preeclampsia prediction in this population would transform antenatal care. To identify novel protein markers relevant to the prediction of preeclampsia, a 3-step mass spectrometric work flow was applied. On selection of candidate biomarkers, mostly from an unbiased discovery experiment (19 women), targeted quantitation was used to verify and validate candidate biomarkers in 2 independent cohorts from the SCOPE (SCReening fOR Pregnancy Endpoints) study. Candidate proteins were measured in plasma specimens collected at 19 to 21 weeks' gestation from 100 women who later developed preeclampsia and 200 women without preeclampsia recruited from Australia and New Zealand. Protein levels ($n=25$), age, and blood pressure were then analyzed using logistic regression to identify multimarker models (maximum 6 markers) that met predefined criteria: sensitivity $\geq 50\%$ at 20% positive predictive value. These 44 algorithms were then tested in an independent European cohort ($n=300$) yielding 8 validated models. These 8 models detected 50% to 56% of preeclampsia cases in the training and validation sets; the detection rate for preterm preeclampsia cases was 80%. Validated models combine insulin-like growth factor acid labile subunit and soluble endoglin, supplemented with maximally 4 markers of placental growth factor, serine peptidase inhibitor Kunitz type 1, melanoma cell adhesion molecule, selenoprotein P, and blood pressure. Predictive performances were maintained when exchanging mass spectrometry measurements with ELISA measurements for insulin-like growth factor acid labile subunit. In conclusion, we demonstrated that biomarker combinations centered on insulin-like growth factor acid labile subunit have the potential to predict preeclampsia in healthy nulliparous women.

Elevation of Angiotensin-II Type-1-Receptor Autoantibodies Titer in Primary Aldosteronism as a Result of Aldosterone-Producing Adenoma³⁵

Abstract

The mechanisms of excess aldosterone secretion in primary aldosteronism (PA) remain poorly understood, although a role for circulating factors has been hypothesized for decades. Agonistic autoantibodies against type-1 angiotensin-II receptor (AT1AA) are detectable in malignant hypertension and preeclampsia and might play a role in PA. Moreover, if they were elevated in aldosterone-producing adenoma (APA) and not in idiopathic hyperaldosteronism (IHA), they might be useful for discriminating between these conditions. To test these hypotheses, we measured the titer of AT1AA in serum of 46 patients with PA (26 with APA, 20 with IHA), 62 with primary hypertension (PH), 13 preeclamptic women, and 45 healthy normotensive blood donors. We found that the AT1AA titer was higher ($P<0.05$) in both PA and PH patients (2.65 ± 1.55 and 1.86 ± 0.63 , respectively) than in normotensive subjects (1.00 ± 0.20). In APA, it was 2-fold higher than in IHA patients (3.43 ± 1.20 versus 1.64 ± 1.39 , respectively, $P<0.001$), despite similar blood pressure values. Of note, it allowed effective discrimination of APA from either PH or IHA, as shown by Receiver Operator Characteristics curve analysis. Moreover, after captopril challenge, plasma aldosterone concentration fell more in AT1AA-positive than in AT1AA-negative PA patients (-32.4% [$21.1-42.9$] versus 0.0% [$0.0-22.6$], $P=0.015$), suggesting an agonistic role for these autoantibodies. Thus, a higher serum AT1AA titer in patients with APA than in IHA and PH patients can be useful in differentiating APA patients from either PH or IHA, and thus in selecting PA patients to be submitted to adrenal vein sampling.

Experimental Hyperleptinemia in Neonatal Rats Leads to Selective Leptin Responsiveness, Hypertension, and Altered Myocardial Function³⁶

Abstract

The prevalence of obesity among pregnant women is increasing. Evidence from human cohort studies and experimental animals suggests that offspring cardiovascular and metabolic function is compromised through early life exposure to maternal obesity. Previously, we reported that juvenile offspring of obese rats develop sympathetically mediated hypertension associated with neonatal hyperleptinemia. We have now addressed the hypothesis that neonatal exposure to raised leptin in the immediate postnatal period plays a causal role. Pups from lean Sprague-Dawley rats were treated either with leptin (3 mg/kg IP) or with saline twice daily from postnatal day 9 to 15 to mimic the exaggerated postnatal leptin surge observed in offspring of obese dams. Cardiovascular function was assessed by radiotelemetry at 30 days, and 2 and 12 months. In juvenile (30 days) leptin-treated rats, hearts were heavier and night-time (active period) systolic blood pressure was raised (mmHg; mean \pm SEM: male leptin-treated, 132 ± 1 versus saline-treated, 119 ± 1 , $n=6$, $P<0.05$; female leptin-treated, 132 ± 2 versus saline-treated, 119 ± 1 , $n=6$, $P<0.01$), and the pressor response to restraint stress and leptin challenge increased compared with saline-treated rats. Heart rate variability demonstrated an increased low:high frequency ratio in 30-day leptin-treated animals, indicative of heightened sympathetic efferent tone. Echocardiography showed altered left ventricular structure and systolic function in 30-day female leptin versus saline-treated rats. These disorders persisted to adulthood. In isolated hearts, contractile function was impaired at 5 months in male leptin-treated rats. Exogenously imposed hyperleptinemia in neonatal rats permanently influences blood pressure and cardiac structure and function.

Microvesicles of Women with Gestational Hypertension and Preeclampsia Affect Human Trophoblast Fate and Endothelial Function³⁷

Abstract

Microvesicles shedding from cell membrane affect inflammation, apoptosis, and angiogenesis. We hypothesize that microvesicles of women with gestational vascular complications reflect pathophysiological state of the patients and affect their endothelial and trophoblast cell function. Microvesicles of healthy pregnant women, women with gestational hypertension, mild, or severe preeclampsia/toxemia, were characterized, and their effects on early-stage or term trophoblasts and endothelial cells were evaluated using apoptosis, migration, and tube formation assays. Patient subgroups differed significantly only in proteinuria levels, therefore their microvesicles were assessed as 1 group, demonstrating higher levels of inflammatory and angiogenic proteins compared with those of healthy pregnant women. In endothelial cells, microvesicles of healthy pregnant women reduced caspase 3/7 activity, increased migration, and induced tube formation. These processes were suppressed by microvesicles of women with gestational vascular complications. In early-stage trophoblasts, microvesicles of healthy pregnant women decreased apoptosis compared with untreated cells ($6\pm 5\%$ versus $13.8\pm 5.8\%$; $P<0.001$) and caspase 3/7 activity and induced higher migration (39.7 ± 10.1 versus 20.3 ± 8.3 mm²; $P<0.001$). This effect was mediated through extracellular signal-regulated kinase pathway. Conversely, microvesicles of women with gestational vascular complications increased term trophoblast apoptosis compared with cells exposed to microvesicles of healthy pregnant women ($15.1\pm 3.3\%$ versus $6.5\pm 2.1\%$; $P<0.001$) and inhibited early-stage trophoblasts migration (21.4 ± 18.5 versus 39.7 ± 10.1 mm²; $P<0.001$). In conclusion, microvesicle content and effects on endothelial and trophoblast cells vary according to the physiological/pathological state of a pregnant woman. Microvesicles seem to play a pivotal role in the course of pregnancy, which could potentially result in gestational vascular complications.

Angiotensin Receptor Agonistic Autoantibody-Mediated Soluble fms-Like Tyrosine Kinase-1 Induction Contributes to Impaired Adrenal Vasculature and Decreased Aldosterone Production in Preeclampsia³⁸

Abstract

Preeclampsia is a life-threatening hypertensive disorder of pregnancy associated with decreased circulating aldosterone levels. However, the molecular mechanisms underlying aldosterone reduction in preeclampsia remain unidentified. Here we demonstrate that reduced circulating aldosterone levels in the preeclamptic women are associated with the presence of angiotensin II type I receptor agonistic autoantibody (AT1-AA) and elevated soluble Fms-like tyrosine kinase-1 (sFlt-1), two prominent pathogenic factors in preeclampsia. Using an adoptive transfer animal model of preeclampsia, we provide *in vivo* evidence that the injection of IgG from women with preeclampsia, but not IgG from normotensive individuals, resulted in hypertension, proteinuria and a reduction in aldosterone production from 1377 ± 272 pg/ml to 544 ± 92 pg/ml ($P < 0.05$) in pregnant mice. These features were prevented by co-injection with an epitope peptide that blocks antibody-mediated AT1 receptor (AT1R) activation. In contrast, injection of IgG from preeclamptic women into non-pregnant mice induced aldosterone levels from 213 ± 24 pg/ml to 615 ± 48 pg/ml ($P < 0.05$). These results indicate that maternal circulating autoantibody in preeclamptic women is a detrimental factor causing decreased aldosterone production via AT1R activation in a pregnancy-dependent manner. Next, we found that circulating sFlt-1 was only induced in autoantibody-injected pregnant mice but not non-pregnant mice. As such, we further observed vascular impairment in adrenal glands of pregnant mice. Finally, we demonstrated that infusion of VEGF121 attenuated autoantibody-induced adrenal gland vascular impairment resulting in a recovery in circulating aldosterone (from 544 ± 92 to 1110 ± 269 pg/ml, $P < 0.05$). Overall, we revealed that AT1-AA-induced sFlt-1 elevation is a novel pathogenic mechanism underlying decreased aldosterone production in preeclampsia.

Explaining Socioeconomic Inequalities in Childhood Blood Pressure and Prehypertension: The ABCD Study³⁹

Abstract

Much remains to be understood about the socioeconomic inequalities in hypertension that continue to exist. We investigated the association of socioeconomic status with blood pressure and prehypertension in childhood. In a prospective cohort, 3024 five- to six-year-old children had blood pressure measurements and available information on potential explanatory factors, namely birth weight, gestational age, smoking during pregnancy, pregnancy-induced hypertension, familial hypertension, maternal body mass index, breastfeeding duration, domestic tobacco exposure, and body mass index. The systolic and diastolic blood pressures of children from mid-educated women were 1.0-mmHg higher (95% confidence interval [CI], 0.4–1.7) and 0.9-mmHg higher (95% CI, 0.3–1.4), and the blood pressures of children with low-educated women were 2.2-mmHg higher (95% CI, 1.4–3.0) and 1.7-mmHg higher (95% CI, 1.1–2.4) compared with children with high-educated women. Children with mid- (odds ratio, 1.50; 95% CI, 1.18–1.92) or low-educated mothers (odds ratio, 1.80; 95% CI, 1.35–2.42) were more likely to have prehypertension compared with children with high-educated mothers. Using path analyses, birth weight, breastfeeding duration, and body mass index were determined as having a role in the association of maternal education with offspring blood pressure and prehypertension. The socioeconomic gradient in hypertension appears to emerge from childhood as the results show a higher blood pressure and more prehypertension in children from lower socioeconomic status families. Socioeconomic disparities could be reduced by improving 3 factors in particular, namely birth weight, breastfeeding duration, and body mass index, but other factors might also play a role.

Maternal Cardiovascular Risk Profile After Placental Abruption⁴⁰

Abstract

The prevalence of premature cardiovascular diseases (CVD) is increased in women with a history of maternal placental syndromes, including pregnancy-associated hypertensive disorders (eg, preeclampsia), fetal growth restriction, and placental abruption. Whereas previous studies have shown a high prevalence of CVD risk factors after pregnancies complicated by preeclampsia, this has not been studied for women with a history of placental abruption. To explore the association of placental abruption with CVD risk factors after delivery, we compared 75 women with a history of placental abruption with a control group of 79 women with uneventful pregnancies at 6 to 9 months postpartum for the presence of common CVD risk factors. In a subanalysis, data were stratified according to the presence or absence of concomitant hypertensive disease and further adjusted for potential confounders. Women with previous placental abruption had significantly higher mean systolic blood pressure, body-mass index, fasting blood glucose, C-reactive protein, total cholesterol, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol as compared with controls with only uneventful pregnancies. In the subanalysis, all differences remained significant for women with a history of placental abruption only (ie, without concomitant gestational hypertension), except for the associations with low-density lipoprotein-cholesterol and diastolic and systolic blood pressure. Most likely, the identified CVD risk factors predispose to placental abruption and development of premature CVD later in life.

Postnatal Sulfur Dioxide Exposure Reversibly Alters Parasympathetic Regulation of Heart Rate⁴¹

Abstract

Perinatal sulfur dioxide exposure disrupts parasympathetic regulation of cardiovascular activity. Here, we examine the relative risks of prenatal versus postnatal exposure to the air pollutant and the reversibility of the cardiovascular effects. Two groups of animals were used for this study. For prenatal exposure, pregnant Sprague–Dawley dams were exposed to 5 parts per million sulfur dioxide for 1 hour daily throughout gestation and with their pups after birth to medical-grade air through 6 days postnatal. For postnatal exposure, dams were exposed to air, and after delivery along with their pups to 5 parts per million sulfur dioxide through postnatal day 6. ECGs were recorded from pups on postnatal day 5 to examine changes in heart rate. Whole-cell patch-clamp electrophysiology was used to examine changes in neurotransmission to cardiac vagal neurons in the nucleus ambiguus on sulfur dioxide exposure. Postnatal sulfur dioxide exposure diminished glutamatergic neurotransmission to cardiac vagal neurons by 40.9% and increased heart rate, whereas prenatal exposure altered neither of these properties. When postnatal exposure concluded on postnatal day 5, excitatory neurotransmission remained decreased through day 6 and returned to basal levels by day 7. ECGs showed that heart rate remained elevated through day 6 and recovered by day 7. On activation of the parasympathetic diving reflex, the response was significantly blunted by postnatal sulfur dioxide exposure through day 7 but recovered by day 8. Postnatal, but not prenatal, exposure to sulfur dioxide can disrupt parasympathetic regulation of cardiovascular activity. Neonates can recover from these effects within 2 to 3 days of discontinued exposure.

Estrogen Normalizes Perinatal Nicotine-Induced Hypertensive Responses in Adult Female Rat Offspring⁴²

Abstract

Perinatal nicotine exposure caused a sex-dependent heightened vascular response to angiotensin II (Ang II) and increased blood pressure in adult male but not in female rat offspring. The present study tested the hypothesis that estrogen normalizes perinatal nicotine-induced hypertensive response to Ang II in female offspring. Nicotine was administered to pregnant rats via subcutaneous osmotic minipumps from day 4 of gestation to day 10 after birth. Ovariectomy and 17 β -estradiol replacement were performed on 8-week-old female offspring. At 5 months of age, Ang II-induced blood pressure responses were not changed by nicotine treatment in the sham groups. In contrast, nicotine significantly enhanced Ang II-induced blood pressure responses as compared with saline control in the ovariectomy groups, which was associated with increased Ang II-induced vascular contractions. These heightened responses were abrogated by 17 β -estradiol replacement. In addition, nicotine enhanced Ang II receptor type I, NADPH (nicotinamide adenine dinucleotide phosphate) oxidase type 2 protein expressions, and reactive oxygen species production of aortas as compared with saline control in the ovariectomy groups. Antioxidative agents, both apocynin and tempol, inhibited Ang II-induced vascular contraction and eliminated the differences of contractions between nicotine-treated and control ovariectomy rats. These findings support a key role of estrogen in the sex difference of perinatal nicotine-induced programming of vascular dysfunction, and suggest that estrogen may counteract heightened reactive oxygen species production, leading to protection of females from development programming of hypertensive phenotype in adulthood.

The Risk of Congenital Malformations Associated With Exposure to Beta-Blockers Early in Pregnancy: A Meta-Analysis⁴³

Abstract

β -Blockers are commonly used during the first trimester of pregnancy. Data about risks of congenital anomalies in offspring have not been summarized. We performed a meta-analysis to determine teratogenicity of β -blockers in early pregnancy. A systematic literature search was performed using PubMed, EMBASE, Cochrane Clinical Trials, and hand search. Meta-analyses were performed using random-effects models based on odds ratios (ORs). Prespecified subgroup analyses were performed to explore heterogeneity. Randomized controlled trials or observational studies examining risks of congenital malformations associated with first trimester β -blocker exposure compared with no exposure were included. Thirteen population-based case-control or cohort studies were identified. Based on meta-analyses, first-trimester oral β -blocker use showed no increased odds of all or major congenital anomalies (OR, 1.00; 95% confidence interval, 0.91–1.10; 5 studies). However, in analyses examining organ-specific malformations, increased odds of cardiovascular defects (OR, 2.01; 95% confidence interval, 1.18–3.42; 4 studies), cleft lip/palate (OR, 3.11; 95% confidence interval, 1.79–5.43; 2 studies), and neural tube defects (OR=3.56; 95% confidence interval, 1.19–10.67; 2 studies) were observed. The effects on severe hypospadias were nonsignificant (1 study). Causality is difficult to interpret given the small number of heterogeneous studies and possibility of biases. Given the frequency of this exposure in pregnancy, further research is needed.

Gestational Hypoxia Induces Preeclampsia-Like Symptoms via Heightened Endothelin-1 Signaling in Pregnant Rats⁴⁴

Abstract

Preeclampsia is a life-threatening pregnancy disorder. However, its pathogenesis remains unclear. We tested the hypothesis that gestational hypoxia induces preeclampsia-like symptoms via heightened endothelin-1 (ET-1) signaling. Time-dated pregnant and nonpregnant rats were divided into normoxic and hypoxic (10.5% O₂ from the gestational day 6–21) groups. Chronic hypoxia had no significant effect on blood pressure or proteinuria in nonpregnant rats but significantly increased blood pressure on day 12 (systolic blood pressure, 111.7±6.1 versus 138.5±3.5 mmHg; *P*=0.004) and day 20 (systolic blood pressure, 103.4±4.6 versus 125.1±6.1 mmHg; *P*=0.02) in pregnant rats and urine protein (μg/μL)/creatinine (nmol/μL) ratio on day 20 (0.10±0.01 versus 0.20±0.04; *P*=0.04), as compared with the normoxic control group. This was accompanied with asymmetrical fetal growth restriction. Hypoxia resulted in impaired trophoblast invasion and uteroplacental vascular remodeling. In addition, plasma ET-1 levels, as well as the abundance of prepro-ET-1 mRNA, ET-1 type A receptor and angiotensin II type I receptor protein in the kidney and placenta were significantly increased in the chronic hypoxic group, as compared with the control animals. Treatment with the ET-1 type A receptor antagonist, BQ123, during the course of hypoxia exposure significantly attenuated the hypoxia-induced hypertension and other preeclampsia-like features. The results demonstrate that chronic hypoxia during gestation induces preeclamptic symptoms in pregnant rats via heightened ET-1 and ET-1 type A receptor-mediated signaling, providing a molecular mechanism linking gestational hypoxia and increased risk of preeclampsia.

Chronic Hypoxia Inhibits Pregnancy-Induced Upregulation of SKCa Channel Expression and Function in Uterine Arteries⁴⁵

Abstract

Small-conductance Ca²⁺-activated K⁺ (SKCa) channels are crucial in regulating vascular tone and blood pressure. The present study tested the hypothesis that SKCa channels play an important role in uterine vascular adaptation in pregnancy, which is inhibited by chronic hypoxia during gestation. Uterine arteries were isolated from nonpregnant and near-term pregnant sheep maintained at sea level (≈300 m) or exposed to high-altitude (3801 m) hypoxia for 110 days. Immunohistochemistry revealed the presence of SKCa channels type 2 (SK2) and type 3 (SK3) in both smooth muscles and endothelium of uterine arteries. The expression of SK2 and SK3 channels was significantly increased during pregnancy, which was inhibited by chronic hypoxia. In normoxic animals, both SKCa channel opener NS309 and a large-conductance (BKCa) channel opener NS1619 relaxed norepinephrine-contracted uterine arteries in pregnant but not nonpregnant sheep. These relaxations were inhibited by selective SKCa and BKCa channel blockers, respectively. NS309-induced relaxation was largely endothelium-independent. In high-altitude hypoxic animals, neither NS1691 nor NS309 produced significant relaxation of uterine arteries in either nonpregnant or pregnant sheep. Similarly, the role of SKCa channels in regulating the myogenic reactivity of uterine arteries in pregnant animals was abrogated by chronic hypoxia. Accordingly, the enhanced SKCa channel activity in uterine arterial myocytes of pregnant animals was ablated by chronic hypoxia. The findings suggest a novel mechanism of SKCa channels in regulating myogenic adaptation of uterine arteries in pregnancy and in the maladaptation of uteroplacental circulation caused by chronic hypoxia during gestation.

References

1. Abdalvand A, Morton JS, Bourque SL, Quon AL, Davidge ST. Matrix metalloproteinase enhances big-endothelin-1 constriction in mesenteric vessels of pregnant rats with reduced uterine blood flow. *Hypertension*. 2013;61:488–493.
2. Ayoola OO, Omotade OO, Gemmill I, Clayton PE, Cruickshank JK. The impact of malaria in pregnancy on changes in blood pressure in children during their first year of life. *Hypertension*. 2014;63:167–172.
3. Bauer AJ, Banek CT, Needham K, Gillham H, Capoccia S, Regal JF, Gilbert JS. Pravastatin attenuates hypertension, oxidative stress, and angiogenic imbalance in rat model of placental ischemia-induced hypertension. *Hypertension*. 2013;61:1103–1110.
4. Brewer J, Liu R, Lu Y, Scott J, Wallace K, Wallukat G, Moseley J, Herse F, Dechend R, Martin JN Jr, Lamarca B. Endothelin-1, oxidative stress, and endogenous angiotensin II: mechanisms of angiotensin II type I receptor autoantibody-enhanced renal and blood pressure response during pregnancy. *Hypertension*. 2013;62:886–892.
5. Burwick RM, Fichorova RN, Dawood HY, Yamamoto HS, Feinberg BB. Urinary excretion of C5b-9 in severe preeclampsia: tipping the balance of complement activation in pregnancy. *Hypertension*. 2013;62:1040–1045.
6. Buurma AJ, Penning ME, Prins F, Schutte JM, Bruijn JA, Wilhelmus S, Rajakumar A, Bloemenkamp KW, Karumanchi SA, Baelde HJ. Preeclampsia is associated with the presence of transcriptionally active placental fragments in the maternal lung. *Hypertension*. 2013;62:608–613.
7. Catov JM, Lewis CE, Lee M, Wellons MF, Gunderson EP. Preterm birth and future maternal blood pressure, inflammation, and intimal-medial thickness: the CARDIA study. *Hypertension*. 2013;61:641–646.
8. Chinnathambi V, Balakrishnan M, Ramadoss J, Yallampalli C, Sathishkumar K. Testosterone alters maternal vascular adaptations: role of the endothelial NO system. *Hypertension*. 2013;61:647–654.
9. Cornelius DC, Hogg JP, Scott J, Wallace K, Herse F, Moseley J, Wallukat G, Dechend R, LaMarca B. Administration of interleukin-17 soluble receptor C suppresses TH17 cells, oxidative stress, and hypertension in response to placental ischemia during pregnancy. *Hypertension*. 2013;62:1068–1073.
10. Craici IM, Wagner SJ, Bailey KR, Fitz-Gibbon PD, Wood-Wentz CM, Turner ST, Hayman SR, White WM, Brost BC, Rose CH, Grande JP, Garovic VD. Podocyturia predates proteinuria and clinical features of preeclampsia: longitudinal prospective study. *Hypertension*. 2013;61:1289–1296.
11. de Jonge LL, Harris HR, Rich-Edwards JW, Willett WC, Forman MR, Jaddoe VW, Michels KB. Parental smoking in pregnancy and the risks of adult-onset hypertension. *Hypertension*. 2013;61:494–500.
12. Doridot L, Passet B, Mehats C, et al. Preeclampsia-like symptoms induced in mice by fetoplacental expression of

- STOX1 are reversed by aspirin treatment. *Hypertension*. 2013;61:662–668.
13. Fraser A, Nelson SM, Macdonald-Wallis C, Sattar N, Lawlor DA. Hypertensive disorders of pregnancy and cardiometabolic health in adolescent offspring. *Hypertension*. 2013;62:614–620.
 14. Fu G, Ye G, Nadeem L, Ji L, Manchanda T, Wang Y, Zhao Y, Qiao J, Wang YL, Lye S, Yang BB, Peng C. MicroRNA-376c impairs transforming growth factor- β and nodal signaling to promote trophoblast cell proliferation and invasion. *Hypertension*. 2013;61:864–872.
 15. Gademan MG, van Eijnsden M, Roseboom TJ, van der Post JA, Stronks K, Vrijkotte TG. Maternal prepregnancy body mass index and their children's blood pressure and resting cardiac autonomic balance at age 5 to 6 years. *Hypertension*. 2013;62:641–647.
 16. Gammill HS, Aydelotte TM, Guthrie KA, Nkwopara EC, Nelson JL. Cellular fetal microchimerism in preeclampsia. *Hypertension*. 2013;62:1062–1067.
 17. Genest DS, Falcao S, Michel C, Kajla S, Germano MF, Lacasse AA, Vaillancourt C, Gutkowska J, Lavoie JL. Novel role of the renin-angiotensin system in preeclampsia superimposed on chronic hypertension and the effects of exercise in a mouse model. *Hypertension*. 2013;62:1055–1061.
 18. Gennari-Moser C, Khankin EV, Escher G, Burkhard F, Frey BM, Karumanchi SA, Frey FJ, Mohaupt MG. Vascular endothelial growth factor-A and aldosterone: relevance to normal pregnancy and preeclampsia. *Hypertension*. 2013;61:1111–1117.
 19. Ghossein-Doha C, Peeters L, van HS, van KS, Spaan J, Delhaas T, Spaanderman M. Hypertension after preeclampsia is preceded by changes in cardiac structure and function. *Hypertension*. 2013;62:382–390.
 20. Intapad S, Tull FL, Brown AD, Dasinger JH, Ojeda NB, Fahling JM, Alexander BT. Renal denervation abolishes the age-dependent increase in blood pressure in female intrauterine growth-restricted rats at 12 months of age. *Hypertension*. 2013;61:828–834.
 21. Janzarik WG, Ehlers E, Ehmman R, Gerds TA, Schork J, Mayer S, Gabriel B, Weiller C, Prömpeler H, Reinhard M. Dynamic cerebral autoregulation in pregnancy and the risk of preeclampsia. *Hypertension*. 2014;63:161–166.
 22. Jobe SO, Ramadoss J, Wargin AJ, Magness RR. Estradiol-17 β and its cytochrome P450- and catechol-O-methyltransferase-derived metabolites stimulate proliferation in uterine artery endothelial cells: role of estrogen receptor- α versus estrogen receptor- β . *Hypertension*. 2013;61:509–518.
 23. Jobe SO, Tyler CT, Magness RR. Aberrant synthesis, metabolism, and plasma accumulation of circulating estrogens and estrogen metabolites in preeclampsia implications for vascular dysfunction. *Hypertension*. 2013;61:480–487.
 24. Kulandavelu S, Whiteley KJ, Bainbridge SA, Qu D, Adamson SL. Endothelial NO synthase augments fetoplacental blood flow, placental vascularization, and fetal growth in mice. *Hypertension*. 2013;61:259–266.
 25. Kvehaugen AS, Melien O, Holmen OL, Laivuori H, Oian P, Andersgaard AB, Dechend R, Staff AC. Single nucleotide polymorphisms in G protein signaling pathway genes in preeclampsia. *Hypertension*. 2013;61:655–661.
 26. László KD, Liu XQ, Svensson T, Wikström AK, Li J, Olsen J, Obel C, Vestergaard M, Cnattingius S. Psychosocial stress related to the loss of a close relative the year before or during pregnancy and risk of preeclampsia. *Hypertension*. 2013;62:183–189.
 27. Leñaos-Miranda A, Campos-Galicia I, Ramírez-Valenzuela KL, Chinolla-Arellano ZL, Isordia-Salas I. Circulating angiogenic factors and urinary prolactin as predictors of adverse outcomes in women with preeclampsia. *Hypertension*. 2013;61:1118–1125.
 28. Li Z, Ye R, Zhang L, Li H, Liu J, Ren A. Folic acid supplementation during early pregnancy and the risk of gestational hypertension and preeclampsia. *Hypertension*. 2013;61:873–879.
 29. Lupton SJ, Chiu CL, Hodgson LA, Toher J, Ogle R, Wong TY, Hennessy A, Lind JM. Changes in retinal microvascular caliber precede the clinical onset of preeclampsia. *Hypertension*. 2013;62:899–904.
 30. Lupton SJ, Chiu CL, Hodgson LA, Toher J, Lujic S, Ogle R, Wong TY, Hennessy A, Lind JM. Temporal changes in retinal microvascular caliber and blood pressure during pregnancy. *Hypertension*. 2013;61:880–885.
 31. Lyall F, Robson SC, Bulmer JN. Spiral artery remodeling and trophoblast invasion in preeclampsia and fetal growth restriction: relationship to clinical outcome. *Hypertension*. 2013;62:1046–1054.
 32. Martillotti G, Ditisheim A, Burnier M, Wagner G, Boulvain M, Irion O, Pechère-Bertschi A. Increased salt sensitivity of ambulatory blood pressure in women with a history of severe preeclampsia. *Hypertension*. 2013;62:802–808.
 33. Mizuno M, Siddique K, Baum M, Smith SA. Prenatal programming of hypertension induces sympathetic overactivity in response to physical stress. *Hypertension*. 2013;61:180–186.
 34. Myers JE, Tuytten R, Thomas G, Laroy W, Kas K, Vanpoucke G, Roberts CT, Kenny LC, Simpson NA, Baker PN, North RA. Integrated proteomics pipeline yields novel biomarkers for predicting preeclampsia. *Hypertension*. 2013;61:1281–1288.
 35. Rossitto G, Regolisti G, Rossi E, Negro A, Nicoli D, Casali B, Toniato A, Caroccia B, Seccia TM, Walther T, Rossi GP. Elevation of angiotensin-II type-I-receptor autoantibodies titer in primary aldosteronism as a result of aldosterone-producing adenoma. *Hypertension*. 2013;61:526–533.
 36. Samuelsson AM, Clark J, Rudyk O, Shattock MJ, Bae SE, South T, Pombo J, Redington K, Uppal E, Coen CW, Poston L, Taylor PD. Experimental hyperleptinemia in neonatal rats leads to selective leptin responsiveness, hypertension, and altered myocardial function. *Hypertension*. 2013;62:627–633.
 37. Shomer E, Katzenell S, Zipori Y, Sammour RN, Isermann B, Brenner B, Aharon A. Microvesicles of women with gestational hypertension and preeclampsia affect human trophoblast fate and endothelial function. *Hypertension*. 2013;62:893–898.
 38. Siddiqui AH, Irani RA, Zhang W, Wang W, Blackwell SC, Kellems RE, Xia Y. Angiotensin receptor agonistic autoantibody-mediated soluble fms-like tyrosine kinase-1 induction contributes to impaired adrenal vasculature and decreased aldosterone production in preeclampsia. *Hypertension*. 2013;61:472–479.
 39. van den Berg G, van Eijnsden M, Galindo-Garre F, Vrijkotte TG, Gemke RJ. Explaining socioeconomic inequalities in childhood blood pressure and prehypertension: the ABCD study. *Hypertension*. 2013;61:35–41.
 40. Veerbeek JH, Smit JG, Koster MP, Post Uiterweer ED, van Rijn BB, Koenen SV, Franx A. Maternal cardiovascular risk profile after placental abruption. *Hypertension*. 2013;61:1297–1301.
 41. Woerman AL, Mendelowitz D. Postnatal sulfur dioxide exposure reversibly alters parasympathetic regulation of heart rate. *Hypertension*. 2013;62:274–280.
 42. Xiao D, Huang X, Yang S, Zhang L. Estrogen normalizes perinatal nicotine-induced hypertensive responses in adult female rat offspring. *Hypertension*. 2013;61:1246–1254.
 43. Yakoob MY, Bateman BT, Ho E, Hernandez-Diaz S, Franklin JM, Goodman JE, Hoban RA. The risk of congenital malformations associated with exposure to β -blockers early in pregnancy: a meta-analysis. *Hypertension*. 2013;62:375–381.
 44. Zhou J, Xiao D, Hu Y, Wang Z, Paradis A, Mata-Greenwood E, Zhang L. Gestational hypoxia induces preeclampsia-like symptoms via heightened endothelin-1 signaling in pregnant rats. *Hypertension*. 2013;62:599–607.
 45. Zhu R, Hu XQ, Xiao D, Yang S, Wilson SM, Longo LD, Zhang L. Chronic hypoxia inhibits pregnancy-induced upregulation of SKCa channel expression and function in uterine arteries. *Hypertension*. 2013;62:367–374.

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